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Preclinical and Clinical Pharmacology of Vinca Alkaloids

Xiao-Jian Zhou and *Roger Rahmani*
INSERM U-278, Faculté de Pharmacie, Marseille, France

Summary

Vinca alkaloids, including vinblastine, vincristine, vindesine and vinorelbine, are widely used antineoplastic drugs, either as single agents or in combination with other drugs. The mechanism of action of these cell cycle-dependent agents is the inhibition of tubulin polymerisation into microtubules. Numerous studies have been conducted in animals and humans, using various *in vivo* and *in vitro* models, to investigate the pharmacological behaviour of this class of antitumour drug.

Studies in cellular pharmacology demonstrate that vinca alkaloids are transported by multiple mechanisms, including passive diffusion and energy- and temperature-dependent active transport systems. Moreover, active efflux of drug is involved in the P-glycoprotein–mediated multidrug resistance to vinca alkaloids. This phenomenon may be modulated, *in vivo* and *in vitro*, by calcium antagonists and calmodulin inhibitors.

The clinical pharmacokinetics of vinca alkaloids after intravenous bolus injection, continuous infusion and oral administration are characterised by a large apparent total volume of distribution, high total plasma clearance and long terminal elimination half-life. Biliary excretion is the main elimination pathway, with low urinary excretion. Pharmacokinetic parameters of vinca alkaloids are time- and dose-dependent, and large inter- and intra-individual variabilities have been observed. Human hepatic P-450IIIA cytochromes are involved in the metabolism of vindesine, vinblastine and probably other vinca alkaloids. Therefore, the possibility of drug-drug interactions must be considered when coadministering drugs in combination cancer chemotherapy.

Development of newer semisynthetic analogues of vinca alkaloids and conjugation of vinca alkaloids with monoclonal antibodies may result in derivatives with increased antitumour activity and less clinical toxicity.

The early empirical uses of *Catharanthus roseus* (Apocynaceae) for controlling haemorrhage, scurvy, toothache, diabetes, and for the healing of chronic wounds, led to the discovery of antitumour alkaloids in this plant (Johnson et al. 1963). Their anorexic and hypoglycaemic properties prompted isolation and characterisation of the alkaloid molecules responsible for such activities. Further studies then demonstrated that these compounds produced severe leucopenia by blocking cellular mitosis of haematopoietic tissues.

1. Chemical Structures of the Natural and Semisynthetic Vinca Alkaloids

About 30 alkaloids have been extracted from the periwinkle, of which only vinleurosine, vinrosidine, vinblastine and vincristine possess marked

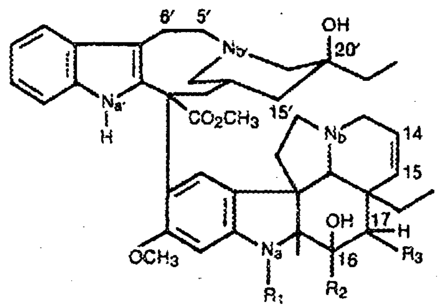

Fig. 1. Chemical structure of the vinca alkaloid nucleus.

antitumour activity. These compounds, especially vinblastine and vincristine, have been widely used as single agents or in combination with other antineoplastic drugs in cancer chemotherapy for more than 20 years. Besides the naturally occurring alkaloids, some vinca alkaloid analogues have been synthesised by functional transformation (vindesine, desacetylvinblastine-amide) [Cersosimo et al. 1983] or, more recently, by semisynthetic processes (vinorelbine, 5'-noranhydrovinblastine) [Mangeney et al. 1979; Maral et al. 1984].

Chemically, these vinca alkaloids have a large dimeric asymmetric structure composed of 2 nuclei linked by a carbon-carbon bond; a dihydroindole nucleus (vindoline), which is the major alkaloid contained in the periwinkle, and an indole nucleus (catharanthine) present in low levels in the plant (fig. 1). The structural differences betweeen vinblastine and vincristine involve the R1 group, while vinblastine and vindesine differ with regard to the R2 and R3 substituents (fig. 2). In contrast with other vinca alkaloids, vinorelbine has structural modifications to the catharanthine nucleus.

2. *Mechanism of Action*

The mode of action of vinca alkaloids has yet to be completely understood; however, it has been established that antitumour activity is directly related to the high binding affinity of these compounds for tubulin, the basic protein subunit of microtubules. It is generally agreed that these agents arrest cell mitosis at metaphase by preventing tubulin polymerisation to form microtubules and by inducing depolymerisation of microtubules, and are therefore cell cycle-dependent antimitotic agents (spindle poisons). The binding constants of vincristine, vinblastine and vindesine for tubulin are 8.0×10^6, 6.0×10^6 and 3.3×10^6 mol/L, respectively (Owellen et al. 1972, 1977a). The inhibition of net tubulin addition by vinca alkaloids has been evaluated at the assembly ends of bovine brain microtubules. The inhibition constants (K_i) were similar for vincristine, vinblastine and vindesine (0.085, 0.178 and 0.110 μmol/L, respectively); however, the K_i values correlated poorly with the ability of the substances to inhibit intact cell growth (Jordan et al. 1985). The major difference between these drugs appeared, therefore, to relate to their retention in tumour tissue (Ferguson et al. 1984, 1985; Singer & Himes 1992). It has been suggested that this is conditioned by the formation and stability of vinca alkaloid-tubulin complexes. In mice bearing human rhabdomyosarcoma xenografts with different sensitivities to vincristine, the formation and stability of vincristine-tubulin complexes in cytosols were guanosine 5'-triphosphate (GTP)-dependent. After removal of endogenous GTP, the initial rate of vincristine binding and the maximal level of bound drug were 2- to 3-fold higher in the presence of 0.1 mmol/L GTP than in its absence; the authors suggested that GTP could have had an important role in the therapeutic selectivity of vinca alkaloids (Bowman et al. 1986; Houghton et al. 1987).

2.1 Comparative Effects of Vinca Alkaloids on Axonal Microtubules

Preclinical and clinical studies demonstrated that vinorelbine has a broader antitumour activity with lower toxicity than vinblastine, vincristine and vindesine; this was thought to be because of the action of vinorelbine on microtubules. The work of Binet et al. (1990), using the tectal plate anlage of mouse embryos at the earliest stages of neuronal differentiation, demonstrated that vinblastine, vincristine and vinorelbine induced depolymerisation of interpolar and mitotic microtubules, and cell

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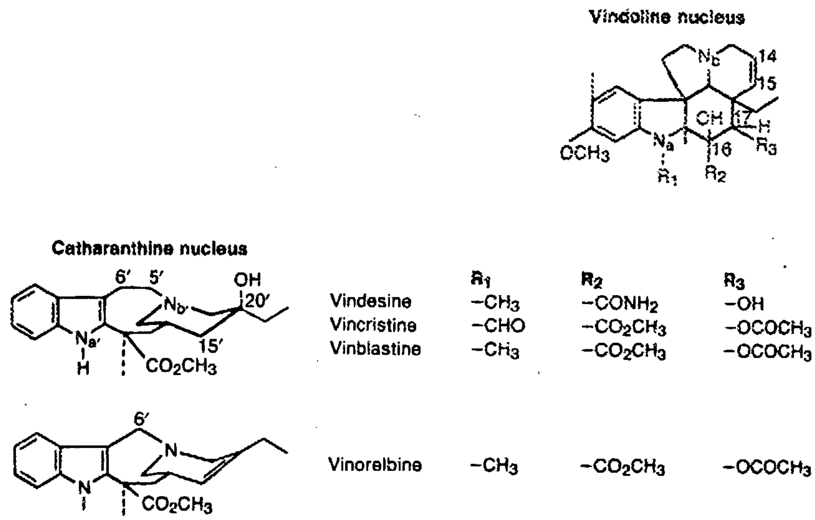

Fig. 2. Structural modifications to the vindoline and catharanthine nuclei in various vinca alkaloids.

blockage at metaphase. Increasing the drug concentrations led to progressive depolymerisation of centromere microtubules; however, only vinorelbine was able to induce complete depolymerisation of these microtubules, resulting in cell arrest at prophase. The activity of these 3 compounds on axonal microtubules was identical; they induced depolymerisation of a labile pool of microtubules. However, this action was dose-related and was observed at higher concentrations of vinorelbine than other vinca alkaloids. Since neurotoxicity may be mediated by spiralisation of axonal microtubules, these data could be related to an improved therapeutic index for vinorelbine, with decreased neurotoxic effects.

3. *Experimental Antitumour Activity*

The cytostatic activity of antitumour vinca alkaloids has been studied by use of various well established animal and human tumour cell lines as well as tumour xenografts. A comparative cytotoxicity study using murine and human tumour cell lines, including murine leukaemia (L1210), human ovarian carcinoma (A2780) and human bronchial epidermoid carcinoma (NSCLC-N6C2), demonstrated that vinorelbine was as active as vinblastine against A2780, less potent than vinblastine and vincristine against L1210, and was more cytotoxic than other vinca alkaloids against NSCLC-N6C2 (Cros et al. 1989; table I).

In a further study using human tumour xenografted *in vivo* in nude mice, vinorelbine was shown to be active against L-27 derived from a human lung carcinoma, whereas vinblastine and vincristine were inactive, when all vinca alkaloids were administered intravenously at equitoxic doses [minimal median survival time of treated mice/median survival time of control mice (T/C) > 0.42]. Similarly, against another human lung carcinoma, LC-06, vinorelbine was more potent than vinblastine and vincristine, and was as active as vindesine. When human stomach tumours (ST-4 and ST-40) were tested, vinorelbine displayed greater activity than other vinca alkaloids (table II).

These *in vitro* and *in vivo* cytotoxicity results have been supported by clinical application of vinca alkaloids. Indeed, vincristine and vindesine are generally used in the treatment of various leukaemias, whereas the main clinical indication for vinorelbine is the treatment of non-small cell lung cancer.

Table I. Comparison of cytotoxicity of vinca alkaloids against murine and human tumour cell lines (after Cros et al. 1989)

Cell lines	IC_{50} (nmol/L)			
	vinorelbine	vinblastine	vincristine	vindesine
Human ovarian carcinoma (A2780)	47.0	42.0	ND	ND
Murine leukaemia (L1210)	7.2	5.0	3.4	ND
Human bronchial epidermoid carcinoma (NSCLC-N6L2)	1.4	2.6	36.0	2.8

Abbreviations: IC_{50} = concentration inhibiting 50% of cell growth; ND = not determined; NSCLC = non-small cell lung cancer.

Table II. Comparative effect of vinca alkaloids on human tumour xenografts (after Cros et al. 1989)

Tumour		Minimal T/C (%)			
origin	line	vinorelbine	vinblastine	vincristine	vindesine
Lung	L-27	0.27	0.48	ND	0.52
Lung	LC-06	0.06	0.25	0.27	0.06
Stomach	ST-4	0.28	0.35	0.44	0.32
Stomach	ST-40	0.21	ND	ND	0.39

Abbreviations: T/C = median survival time of treated mice (T) divided by median survival time of control mice (C); ND = not determined.

4. *Mechanism of Transport*

Numerous *in vitro* studies have been conducted with animal or neoplastic cells to elucidate the mechanism of transport of vinca alkaloids. Irrespective of the model used, they appeared to be intensely and rapidly taken up into cells; however, there were marked differences between the alkaloids. In suspensions of freshly isolated rat hepatocytes, vinblastine was more intensively accumulated in the cells than vincristine or vindesine (Rahmani et al. 1990; Zhou et al. 1990). Similar results were obtained using human hepatocytes, in which the intensity of cellular accumulation of vinca alkaloids appeared to be directly proportional to their liposolubility. Moreover, the intracellular drug concentration was much higher than the extracellular one (Cano et al. 1988). In murine leukaemia cells, the intracellular vincristine concentration was 5- to 20-fold higher than the extracellular concentration (Bleyer et al. 1975). Similar results have been reported with murine lymphoma cell lines (Hela and S49) and a human leukaemic cell line (HL 60), the ratio of intracellular to extracellular drug concentrations varying from 150 to 500 for vinca alkaloids (Ferguson et al. 1984, 1985).

Multiple mechanisms have been described for the transmembrane passage of vinca alkaloids. Some authors have reported an energy- and temperature-dependent active transport; the Michaelis-Menten transport constant (K_m) for vincristine is 6.45 μmol/L in a human leukaemic cell line (CEM/CCRI) and 9.2 μmol/L in murine leukaemic cell lines (L1210, P388) [Beck 1983; Bleyer et al. 1975]. Our own results, obtained by using purified plasma membrane vesicles prepared from rat liver, demonstrated that vinorelbine-binding abilities (from 0.01 to 0.03 μmol/L) accounted for 39 to 48% of total uptake. Transport of vinorelbine was intense and rapid, and primarily occurred by a temperature-independent and unsaturable process (consistent with a simple diffusion mechanism), which accounted for the majority of transportation. A secondary mechanism involved a temperature-dependent saturable transport system. This process was in accord with Michaelis-Menten ki-

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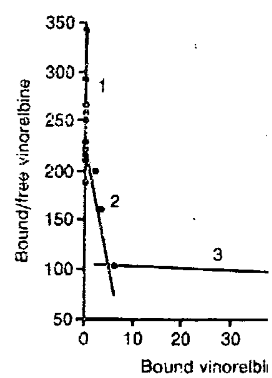

Fig. 3. Scatchard analysis of
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Rahmani-Jourdeuil et al. 19

netics, exhibiting 3 heterogeneous high-affinity binding sites (K_{d1} = 0.1 μmol/L, K_{d2} = 16.5 μmol/L, K_{d3} = 55 μmol/L) [fig. 3].

5. In Vitro *Biotransformation*

The metabolism of vinca alkaloids has been studied *in vitro* using freshly isolated human and animal hepatocytes in suspension, and hepatic subcellular fractions such as microsomes. When incubated in suspensions of rat hepatocytes, vinblastine, vincristine and vindesine were almost completely converted into several metabolites, which were rapidly excreted into the extracellular medium. The intracellular medium contained almost exclusively unchanged drug (more than 85% of total intracellular drug), presumably bound to tubulin protein (Rahmani et al. 1990; Zhou et al. 1990). A large variability in vinca alkaloid metabolism was observed when these compounds were incubated with hepatic microsomal fractions from different species (rat, rabbit, dog, pig, baboon, and human). Similarly, by using a bank of 30 different human hepatic microsomes, the biotransformation of vinca alkaloids presented significant interindividual variability (fig. 4), which may partially explain the clinical pharmacokinetic characteristics of these drugs (Zhou et al. 1992). Recently, using this bank of microsomes, we demonstrated that

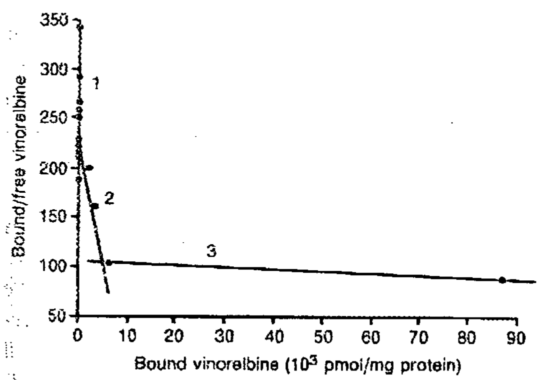

Fig. 3. Scatchard analysis of the vinorelbine transport systems showing that there are 3 binding sites (marked 1, 2 and 3) associated with 3 different dissociation constants (after Rahmani-Jourdeuil et al. 1991).

human hepatic P-450IIIA cytochromes were predominantly involved in the biotransformation of vindesine and vinblastine, and probably all vinca alkaloids.

Since vinca alkaloids are frequently administered in combination with other antineoplastic drugs, potential metabolic drug interactions have been evaluated. Results indicated that some drug classes such as the epipodophyllotoxins (e.g. etoposide, teniposide) significantly inhibited vinca alkaloid metabolism (Zhou et al. 1992). These findings will aid optimisation of combination chemotherapy protocols.

6. *Multidrug Resistance*

The clinical use of vinca alkaloids has led to the development of resistant tumour cells, which has limited effective cancer chemotherapy with these agents. Furthermore, cells selected for resistance to vinca alkaloids also exhibit cross-resistance to a variety of other structurally unrelated 'natural' compounds such as anthracyclines and epipodophyllotoxins, despite no previous exposure to these drugs (Bech-Hansen et al. 1976; Carlsen et al. 1976). This is a major feature of the phenomenon known as pleiotropic or multidrug resistance (MDR) [Beck 1983; Ling et al. 1983], which appears to result from decreased intracellular drug retention, due to an enhanced efflux (Dalton et al. 1986; Dano 1973; Inaba & Johnson 1977). For a given extracellular drug concentration, multidrug-resistant cells maintain a lower intracellular drug concentration than sensitive parental cells.

Numerous studies have been done to determine the origin of MDR by detecting biochemical alterations in multidrug-resistant cells compared with intact cells. The most consistent change is the overexpression of a high molecular weight (170kD) surface plasma membrane glycoprotein, named P-glycoprotein (Gp-170) in multidrug-resistant cells (Beck et al. 1979; Biedler & Peterson 1981; Bosmann 1971; Juliano & Ling 1976; Kartner et al. 1983). In vinblastine-resistant human leukaemia cells, a surface glycoprotein with a molecular weight of 180 to 210kD was detected by use of mono-

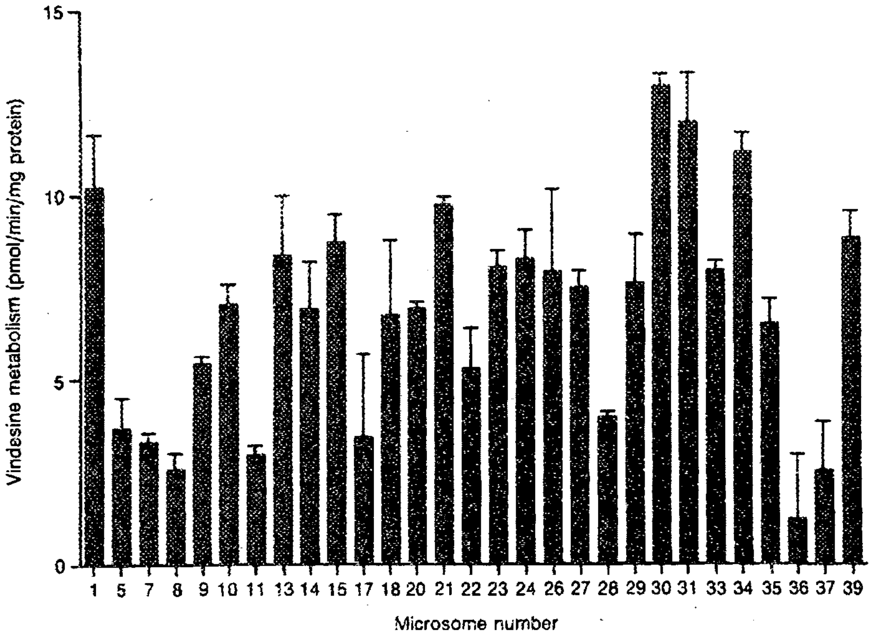

Fig. 4. Interindividual variability in vindesine metabolism on human hepatic microsomal fractions (after Zhou et al. 1992).

clonal antibodies (Danks et al. 1985). The P-glycoprotein was found to be a receptor for vinca alkaloids, and tumour cell drug resistance appeared to be proportional to the amount of P-glycoprotein. Structural analysis of P-glycoprotein demonstrated that it is a conserved integral plasma membrane protein with structural features characteristic of an energy-dependent plasma membrane transport system (Fry et al. 1986; Walker et al. 1982). Moreover, it has been suggested that P-glycoprotein binds adenosine triphosphate (ATP) and couples ATP hydrolysis to its respective energy-requiring biological processes (Higgins et al. 1986). Therefore, one of the dominant mechanisms for resistance to vinca alkaloids or other drug classes could be the reduced intracellular drug retention after P-glycoprotein–mediated, energy-dependent, drug efflux. However, some multidrug-resistant phenotypes have appeared to be P-glycoprotein-independent. Vinca alkaloid-resistant human leukaemic lymphoblast cells (CCRI-CEM) treated with pronase or tunicamycin (an inhibitor of P-glycoprotein), which resulted in the absence of resistance-associated glycoprotein, continued to express resistance to these drugs (Beck & Cirtain 1982). Moreover, therapy-induced resistance of a human leukaemic cell line (LALW-2) to vinca alkaloids has also been shown to be independent of P-glycoprotein (Haber et al. 1989). Gene amplification appears to be the basis for increased expression of P-glycoprotein in highly resistant cell lines. The amplified DNA detected in multidrug-resistant cell lines contains the P-glycoprotein multigene family (*mdr1* gene) [Van der Blick et al. 1986]. Usually, only 1 subset of the *mdr1* gene members is highly amplified in different multidrug-resistant cell lines (De Bruijn et al. 1986; Riordan et al. 1985). Two of this gene family, *mdr1a* and *mdr1b*, encode the 120 and 125kD P-glycoprotein precursors, respectively, in the multidrug-resistant murine J744.2 cell line. The P-glycoprotein encoded by *mdr1a* is functionally more efficient than the form encoded by *mdr1b*, either of which may be overexpressed in multidrug-resistant cells (Lothstein et al. 1989).

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Clinically, MDR has generally been circumvented by combination therapy or by the use of drugs to which the cancer cells are not cross-resistant. Since tumour cell lines have been shown to exhibit low cross-resistance between vinorelbine and other vinca alkaloids, the use of this drug may limit the development of multidrug-resistant cell lines (Maral et al. 1981). So far, however, published data on MDR reversal have essentially focused on screening molecules without antitumour activity or toxicity by means of experimental cellular or tumoral models. Since, in most cases, the development of the multidrug-resistant phenotype is directly related to the overexpression of the surface P-glycoprotein, which actively extrudes intracellular drugs, many of the molecules that could overcome resistance are cellular membrane active agents such as calcium antagonists and calmodulin inhibitors. Verapamil, a calcium antagonist with coronary vasodilator activity, is known to be very potent at enhancing vinca alkaloid cellular accumulation *in vitro* and *in vivo*. The ability of verapamil to overcome MDR was first observed in multidrug-resistant murine P388 cell lines, in which vincristine and vinblastine intracellular concentrations were greatly increased in the presence of verapamil (Tsuruo et al. 1981). The effect was found to be greater for vinca alkaloids than for the other 'natural' drugs such as anthracyclines and epipodophyllotoxins (Beck et al. 1986).

Calmodulin is a regulatory protein of the assembly-disassembly processes of microtubules, which are formed by the polymerisation of tubulin, the most important target of vinca alkaloids (Welsh et al. 1979). Therefore it is reasonable to expect that the vinca alkaloid-resistance of cell lines or human tumour cells may be modulated by the calmodulin inhibitors, prenylamine, trifluoperazine, and clomipramine. In the presence of these agents at 6.6 μmol/L, vincristine cytotoxicity increased 29- to 45-fold in vincristine-resistant human erythroleukaemia (K562) cells. The enhancement of vincristine accumulation appeared to be related to the enhancement of vincristine cytotoxicity by these agents; however, it did not always correlate directly with the cytotoxic effect. Trifluoperazine and clomipramine led to high vincristine accumulation in vincristine-resistant K562 cells, while prenylamine induced a lower accumulation of vincristine. However, prenylamine caused greater enhancement of vincristine cytotoxicity (Tsuruo et al. 1983). A number of other drugs, including flunarizine, reserpine, vitamin A, cepharantine, cefoperazone, quinidine, cyclosporin and its analogues, hexamethylene bisacetamide and some vinca alkaloids without antitumour activity, have also been reported to reverse vinca alkaloid-related multidrug-resistant phenotypes (Ford & Hait 1990).

The mechanism of these drugs in overcoming MDR is not fully elucidated. However, verapamil, trifluoperazine, quinidine, reserpine and cyclosporin share some or all of the features of the known substrates of the P-glycoprotein, including lipophilicity, a planar polycyclic stereochemistry and weak basic properties. These agents appear to reduce or overcome the multidrug resistant phenotype by acting as substrates for the active efflux pump mediated by the P-glycoprotein, competitively inhibiting the active efflux of cytotoxic drugs, thereby increasing intracellular drug accumulation and cytotoxicity. However, it appears necessary to maintain constant intracellular concentrations for the entire time during which cells are exposed to the cytotoxic agent. The calcium antagonists have proven more active than the calmodulin inhibitors in circumvention of MDR. To date, these agents have not been used successfully in clinical practice, since the concentrations required to overcome MDR *in vitro* often lead to severe side effects (such as cardiac disturbances) *in vivo*.

7. Pharmacokinetic Properties of Vinca Alkaloids

7.1 Analytical Methods

Pharmacokinetic studies of vinca alkaloids were initially conducted with radiolabelled drugs, and their concentrations in biological fluids calculated according to the radioactivity; however, this technique could not distinguish unchanged drug from metabolites and/or degradation products, making the results less reliable than currently available as-

say techniques. Radioimmunoassay (RIA) and enzyme-linked immunosorbent assay (ELISA) methods have greatly facilitated the clinical pharmacokinetic investigation of these compounds and have enabled their re-evaluation. These immunological assay methods present various advantages with regard to specificity, sensitivity, and reproducibility, so that they are now the standard assay methods used.

RIA methods using [^{125}I]-labelled probes as antigen have been successfully applied in vindesine and vinorelbine pharmacokinetic evaluations (Rahmani et al. 1983, 1984a). A highly specific RIA for vincristine without cross-reactivity for vinblastine exists (Huhtikangas et al. 1987), and a new ELISA method with a detection limit of 5 nmol/L has been used to re-evaluate the clinical pharmacokinetics of vinblastine (Hacker et al. 1984). In addition, antibodies used for RIA were generally produced in rabbits, but now more specific and sensitive antibodies may be produced using monoclonal techniques (Pontarotti et al. 1985).

Other techniques have been developed, including high performance liquid chromatography (HPLC) [Bloemhof et al. 1991; De Smet et al. 1985; Jehl et al. 1990; Vendrig et al. 1988a,b], which is able to separate unchanged drug from its metabolites. Advances in the field of extraction (solid phase) and detection (electrochemical and fluorescence) techniques make this method applicable for clinical pharmacokinetic studies of vinca alkaloids.

7.2 Clinical Pharmacokinetics

In cancer chemotherapy, the vinca alkaloids have usually been administered by direct intravenous injection at doses of 1 to 2, 1.5 to 6, 7 to 11, and 15 to 30 mg/m^2 for vincristine, vinblastine, vindesine, and vinorelbine, respectively. The pharmacokinetics of vinca alkaloids can generally be described by an open 3-compartment model, which was used to derive pharmacokinetic parameters (Rahmani et al. 1988; fig. 5). The clinical pharmacokinetics of vinca alkaloids have been characterised by a large volume of distribution, a high systemic clearance, and a long terminal eliminat-

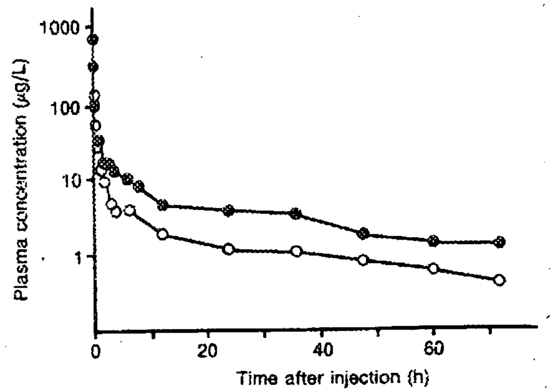

Fig. 5. Plasma pharmacokinetics of vindesine (8 mg/m^2; ○) and vinorelbine (30 mg/m^2; ●) in patients after intravenous injection (after Rahmani et al. 1988).

ion half-life with large inter-molecule and inter- and intra-individual variability in pharmacokinetic parameters. While the initial and intermediate phase half-lives of these agents were similar after intravenous injection, there was a marked difference in the apparent terminal-phase half-lives: 85 hours for vincristine, about 24 hours for vinblastine and vindesine (Nelson et al. 1982) and 40 hours for vinorelbine (Rahmani et al. 1986, 1987) [table III]. The long terminal elimination half-life of vincristine associated with its lower elimination constant may explain its lower maximum tolerated dose compared with other vinca alkaloids. Moreover, the percentages of central compartment distribution volume were higher for vincristine (33%) and vinblastine (69%) than for vindesine (5.4%), suggesting that the latter binds less rapidly to formed blood elements than vincristine and vinblastine (Nelson et al. 1982). Similarly, the relatively high distribution volume of these compounds reflects their large tissue distribution (table III).

The vinca alkaloids are cell cycle-dependent antimitotic agents with narrow therapeutic windows. Intravenous injection leads to very high initial plasma drug concentrations (several hundred μg/L), which may cause more toxic than therapeutic effects. In comparison with intravenous injection,

Table III. Pharmacokinetic parameters of vinca alkaloids in patients after intravenous injection

	Vinblastine		Vincristine		Vindesine			Vinorelbine			
	RIA	RIA	RIA	RIA	RIA	RIA	RIA	RIA	RIA	RIA	HPLC
Dose (mg/m^2)		7-14	3	2	1.5-4	2.5	0.4-8		15-30	30	30
$t_{1/2}\lambda_1$ (h)	0.065	0.062	0.056	0.077	0.054	0.037			0.067		0.134
$t_{1/2}\lambda_2$ (h)	0.88	1.64	2.58	2.27	1.65	0.912			1.82		2.08
$t_{1/2}\gamma$ (h)	19.5	24.8		85.0	20.2	24.2	22.7	31.2	35.0	79.8	42.0

Table III. Pharmacokinetic parameters of vinca alkaloids in patients after intravenous injection

	Vinblastine		Vincristine		Vindesine			Vinorelbine			
	RIA	RIA	RIA	RIA	RIA	RIA	RIA	RIA	RIA	RIA	HPLC
Dose (mg/m^2)		7-14	3	2	1.5-4	2.5	0.4-8		15-30	30	30
$t_{½}\lambda_1$ (h)	0.065	0.062	0.056	0.077	0.054	0.037			0.067		0.134
$t_{½}\lambda_2$ (h)	0.88	1.64	2.58	2.27	1.65	0.912			1.82		2.08
$t_{½}\gamma$ (h)	19.5	24.8		85.0	20.2	24.2	22.7	31.2	35.0	79.8	42.0
V_c (L/kg)	0.28	0.69		0.33	0.084	0.054					
V_z (L/kg)	25.2	27.3		8.4	11.2	8.8		51.4	26.9		75.6
CL (L/h/kg)		0.740		0.106			0.519	0.920	0.756	0.418	1.26
Ae (% of total dose)			9.5		13.2		4.2		3.8	24.6	10.9
Reference no.	1	2	1	2	1	2	3	4	5	6	7

Abbreviations: RIA = radioimmunoassay; HPLC = high performance liquid chromatography; $t_{½}\lambda_1$ = half-life of first phase; $t_{½}\lambda_2$ = half-life of second-phase; $t_{½}\gamma$ = terminal elimination half-life; V_c = apparent volume of distribution of central compartment; V_z = apparent volume of distribution during the terminal phase; CL = clearance of drug from plasma; Ae = amount of unchanged drug excreted into urine.

Reference key: 1 Owellen et al. (1977b); 2 Nelson et al. (1982); 3 Rahmani et al. (1984b); 4 Rahmani et al. (1986); 5 Rahmani et al. (1987); 6 Boré et al. (1989); 7 Jehl et al. 1991.

continuous infusion may be advantageous, because it avoids the toxic peak concentrations and may increase the duration of exposure of cells to the effective concentration (Brade 1981). The steady-state plasma concentration after infusion of vinca alkaloids is in the range of a few μg/L, which seems to be effective because of the high affinity of these agents for tubulin. Increased antitumour activity, with little or no increase in toxicity after continuous infusion of vinca alkaloids has been reported: high remission rates resulted from long-term infusion of vindesine or vinorelbine in patients with haematological malignancies, breast cancer, or head and neck cancer, even when bolus injection had failed (table IV; Bodey et al. 1980; Hande et al. 1980; Mathé et al. 1981). Steady-state levels of 6 to 15 μg/L were achieved with vindesine (Rahmani et al. 1985); this concentration has been shown to produce cytotoxic effects on mammalian cell cultures. For vinblastine, steady-state plasma concentrations of 1.5 to 2 μg/L prevented severe myelosuppression (Ratain & Vogelzang 1986). The dosages administered by continuous infusion were 0.5 to 1, 1.2 to 2, and 0.8 to 1.5 mg/m^2/day for vincristine, vinblastine, and vindesine, respectively. In addition, a significant circadian variation in the plasma vindesine concentration was observed during a 48-hour 1.5 mg/m^2/day continuous infusion in 9 patients (Focan et al. 1989). This finding is of importance with regard to schedule optimisation for drugs with a long terminal half-life. The systemic clearance of vincristine (Jackson et al. 1981), vinblastine (Lu et al. 1983; Ratain et al. 1987) and vindesine (Rahmani et al. 1985) has been reported to decrease during the infusion period compared with intravenous injection. This schedule-dependent systemic clearance could be explained by nonlinear pharmacokinetics, which appear to be a general feature of vinca alkaloids; nonlinearity was strongly suggested by the apparent dose- and/or time-dependence of vindesine and vinorelbine pharmacokinetics after bolus doses (Rahmani et al. 1984b, 1986).

All available data show a large intra- and interpatient variability in pharmacokinetic parameters for vinca alkaloids. This could result from indi-

Table IV. Comparison of response rates and toxicities of bolus injection versus continuous infusion of vindesine

	Refractory breast cancer[1]		Pretreated melanoma, NSCLC[2]		Leukaemia, haematosarcoma[3]		
	bolus	infusion	bolus	infusion	bolus	infusion	infusion
Doses (mg/m^2/day)	3-5 every 10d	1.0-1.2 × 5d 1.4-1.5 × 5d every 3 weeks	3.0 × 2d every 2 weeks	3.0 every week	2.0 × 2d every week	2.0 × 2d after failure of bolus	2.0 × 2d as first treatment
No. of responses/no. of patients treated							
Complete response					10/43	2/12	0/3
Partial remission	1/23	6/21	1/17		6/43	4/12	1/3
No cure	4/23	10/21	2/17	1/9			
No. of patients with toxicity/no. of patients treated							
Paraesthesia	13/52	14/110	8/17	0.9			
Reflexes decreased	13/52	7/110					
Muscle weakness	4/52	7/110					
Haematology							
WBC (× 10^9/L)[a]	2.6-3.3	1.5-2.0	< 3.0 (8/17)[b]	< 3.0 (4/9)[b]			
Platelets (× 10^9/L)[a]	173-200	198-201	< 100 (0/9)[b]	< 100 (1/17)[b]			

a Values are given as ranges.
b No. of patients with toxicity/no. of patients treated.
Abbreviations: NSCLC = non-small cell lung cancer; WBC = white blood cell.
Reference key: 1 Bodey et al. (1980); 2 Hande et al. (1980); 3 Mathé et al. (1981).

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Table V. Relationship betw

Vinca alkaloids
Vinblastine
Vincristine
Vinorelbine
Sodium-formyl vinorelbine
Desacetyl-vinorelbinamide

Abbreviations: LD_{10} = dose
Reference key: 1 Rahmani

vidual differences in hepatic drug disposition and metabolism (Jackson et al. 1981; Van den Berg et al. 1982) and undefined time- and/or dose-dependencies observed after administration (Rahmani et al. 1986, 1987; Zhou et al. 1991). In a group of 24 patients treated with vinblastine by bolus injection followed by prolonged (for 2 to 36 weeks) continuous infusion, the interpatient differences in serum albumin levels were correlated with both the bolus clearance (r = 0.49) and the initial infusion clearance (r = 0.39). Intrapatient variation in vinblastine clearance was positively correlated with albumin and negatively correlated with dose (Ratain et al. 1987). Moreover, the systemic clearance of vincristine, vinblastine and vindesine was found to be significantly correlated with weekly dosages (Nelson et al. 1982) and to parallel toxicity. Because of this, some authors have tried to establish relationships between chemical structure and pharmacokinetic parameters. In general, the 5′-noranhydro modification of the original catharanthine ring increases clearance, while changes to a formyl substituent on the vindoline ring reduces clearance and increases the terminal elimination half-life (Rahmani et al. 1986). Toxicities, and possibly antitumour activities, are related to changes in clearance (Maral et al. 1981, 1984; Todd et al. 1976) [table V].

The large volume of distribution of vinorelbine and its high affinity for tubulin suggest that continuous exposure to low concentrations may be effective and could easily be achieved by oral administration. Recent results obtained in phase I studies of this drug demonstrated that oral vinorelbine was rapidly absorbed and had a good bioavailability (about 40%) [Rahmani et al. 1991]. The relatively high bioavailability could be related to its high liposolubility. Moreover, oral administration of vinorelbine resulted in a pharmacokinetic profile and antitumour activity that were similar to those with intravenous injection, and could therefore represent a new drug delivery pathway for antitumour vinca alkaloids in ambulatory cancer chemotherapy (Zhou et al. 1991).

In human subjects, the vinca alkaloids are largely metabolised and eliminated via the hepatobiliary system. In 2 patients treated with [^{3}H]-vinorelbine, Boré et al. (1989) reported the presence of circulating metabolites, as shown by large discrepancies between plasma concentrations determined by RIA and direct counts of radioactivity: results from one patient are shown in figure 6. Faecal drug excretion within 21 days represented 46.2% of total dose, while urinary excretion was 24.6%. Urinary excretion of vinorelbine was, however, slightly higher than with other vinca alkaloids; urinary excretion was reported to be about 10% of the total dose for vinblastine and vindesine (Rahmani et al. 1984b). However, only desacetyl vinblastine (Owellen et al. 1977b) and desacetyl vinorelbine (Jehl et al. 1991) have been identified as urinary metabolites of vinblastine and vinorelbine, respectively.

Table V. Relationship between clearance and toxicity of vinca alkaloids in animal models

Vinca alkaloids	Mean (± SD) clearance (L/kg • h)[1]	Mean (± SD) LD_{50} (mg/kg)		Mean LD_{10} (mg/kg)[3]
		rat	mouse	mouse
Vinblastine	1.2 ± 0.4	2.9 ± 1.5[2]	10.3 ± 0.8[2]	10.0
Vincristine	0.13 ± 0.5	1.0 ± 0.1[2]	2.1 ± 0.1[2]	1.4
Vinorelbine	2.1 ± 0.5		24.9[3]	20.0
Sodium-formyl vinorelbine	0.27 ± 0.14		6.0[3]	
Desacetyl-vinorelbinamide	2.4 ± 0.7		17.0[3]	

Abbreviations: LD_{10} = dose resulting in death of 10% of animals; LD_{50} = median lethal dose.
Reference key: 1 Rahmani et al. 1986; 2 Todd et al. 1976; 3 Maral et al. 1984.

a Values are given as ranges.
b No. of patients with toxicity/no. of patients treated.
Abbreviations: NSCLC = non-small cell lung cancer; WBC = white blood cell.
Reference key: 1 Bodey et al. (1980); 2 Hande et al. (1980); 3 Mathé et al. (1981).

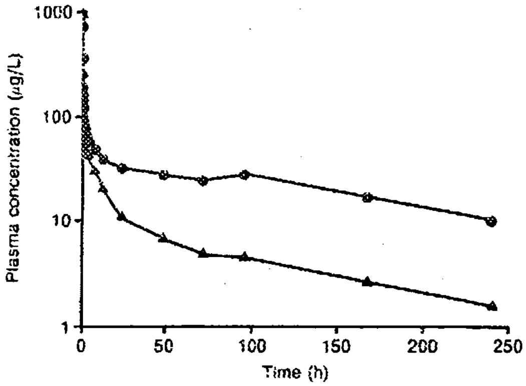

Fig. 6. Plasma pharmacokinetics of vinorelbine in a patient after the administration of 30 mg/m^2 (49.5mg) of [^{3}H]-vinorelbine: evidence for the presence of circulating vinorelbine-related metabolites; ● = direct counts of radioactivity; ▲ = radioimmunoassay (after Boré et al. 1989).

8. *Clinical Efficacy and Tolerability of Vinca Alkaloids*

8.1 Efficacy

Significant differences have been observed in the antitumour activity and toxicity of vinca alkaloids. Vinblastine is usually used to treat Hodgkin's and non-Hodgkin's lymphomas and some solid tumours, including testicular and breast cancer. Vincristine exhibits substantial activity against Hodgkin's and non-Hodgkin's lymphomas, acute lymphoblastic leukaemia, breast carcinoma, Wilm's tumour, Ewing's sarcoma, neuroblastoma, hepatoblastoma and embryonal rhabdomyosarcoma. The antitumour activity of vindesine was found to be similar to that of vinblastine and vincristine, and it is generally used in the treatment of childhood acute lymphocytic leukaemia, acute granulocytic leukaemia, small cell lung cancer and non-Hodgkin's lymphomas. Clinical trials demonstrated that vinorelbine was highly effective in at least 4 categories of cancer: non-small cell lung cancer, breast cancer, ovarian cancer and Hodgkin's disease.

In addition, it has been reported that vinca alkaloid administration led to high platelet counts (Retsas et al. 1978), which appeared to be particular to the alkaloids and was used with success in the management of idiopathic thrombocytopenic purpura and autoimmune thrombocytopenia.

8.2 Tolerability

The toxicity of vinca alkaloids has been extensively studied. Vincristine administration has resulted in disturbances of the central, peripheral and autonomic nervous systems, characterised by a decrease in deep tendon reflexes, paraesthesias, constipation, myalgias, muscle weakness and paralytic ileus (Brade 1981; Legha 1986). Administration of vinblastine and vindesine has led mainly to haematological toxicities, including anaemia and leucopenia (Cersosimo et al. 1983). In addition, these agents have commonly induced alopecia and gastrointestinal disturbances. With vinorelbine, neurotoxicity has been very mild and generally limited to a decrease in or abolition of the osteotendinous reflex. Paraesthesia and cases of paralytic ileus have been rare with this agent. The major dose-limiting factors are leucopenia for vinblastine, vindesine and vinorelbine, and neurotoxicity for vincristine. The neurotoxic symptoms induced by these agents appear to be dose- and time-dependent and generally resolve with dose reduction or treatment withdrawal.

9. *Analogue Development*

Efforts continue to be devoted to the development of new analogues of vinca alkaloids. Vinzolidine is a semisynthetic analogue of vinblastine. Given orally, this compound has marked cytotoxicity against lymphoma cells; however, phase II trials revealed side effects such as severe bone marrow toxicity (Budman et al. 1984). The coupling of vinca alkaloids with amino acids has led to some interesting analogues. Vinca-23-oyl amino acid derivatives, *l*-tryptophan-o-esters and deoxy-o-esters were found to have superior chemotherapeutic activity and diminished toxicity compared with the parent compound in experimental systems (Rao et al. 1985). More recently, 2 vinblastine analogues, S 12363 and S 12362, have been synthesised by

grafting an optically a
the C23 position of
12363 was as potent a
than vinblastine in in
tion *in vitro;* howeve
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found to be 7- to 553-
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grafting an optically active α-aminophosphonate at the C23 position of 04-desacetyl vinblastine. S 12363 was as potent as vincristine, and less potent than vinblastine in inhibiting tubulin polymerisation *in vitro*; however, when tested on a panel of 2 murine and 6 human tumour cell lines, it was found to be 7- to 553-fold and 12- to 74-fold more cytotoxic than vincristine and vinblastine, respectively. S 12362, which differs from S 12363 only by the configuration of the asymmetrical carbon atom of the side chain, was 18- to 59-fold less toxic compared with its isomer. When administered intravenously or intraperitoneally in mice bearing P388 ascites tumour and B16 melanoma, S 12363 was at least as active as vincristine and vinblastine, while the optimal dose was 10- to 20-fold lower (0.15 to 0.20 mg/kg *vs* 2 to 5 mg/kg). Thus, S 12363 has been considered to be the most potent derivative. Its high potency could in part be accounted for by properties conferred by the α-aminophosphonic acid, such as facilitated uptake and/or better cellular retention (Pierré et al. 1990).

Monoclonal antibody (MAb)-antitumour drug conjugates have gained considerable attention as potentially useful tools for the treatment of various human cancers. It is predicted that MAbs, selected specifically to bind particular tumour-associated surface antigens, will preferentially concentrate the attached cytotoxic agents at or within a tumour mass. A number of MAb-vinca alkaloid conjugates have been synthesised and found to be active in both *in vitro* and *in vivo* models. A conjugate composed of the adenocarcinoma-reactive MAb KS1/4S2, coupled through its lysine amino groups to the 4-hydroxy group of the 4-desacetylvinblastine via a succinate bridge, containing 4 to 6 desacetylvinblastine molecules per molecule of KS1/4S2, exhibited a significant antitumour effect *in vivo* against human lung and colorectal adenocarcinoma xenografts in nude mice (Spearman et al. 1987). Pharmacokinetic evaluation (in rats and monkeys) indicated that the conjugate circulated mostly in the intact form in the plasma and was catabolised in the liver, with the subsequent excretion of vinca metabolites into the bile (Marshall et al. 1987). Recently, other conjugates composed of a variety of murine MAbs coupled to desacetylvinblastine hydrazide have been synthesised and found to exhibit potent antitumour activity *in vivo* against a number of human solid tumour xenografts in nude mice, with increased efficacy and safety compared with unconjugated desacetylvinblastine hydrazide or MAb (Lazuzza et al. 1989).

10. Conclusions

The vinca alkaloids continue to be frequently used as single agents or in combination with other drugs in routine cancer chemotherapy. Although their antitumour mechanisms, clinical activity and toxicity have been well defined, mechanisms of drug resistance, nature of transport, and metabolic pathways require further investigation. Some studies on MDR in either a clinical setting (Cantwell et al. 1988) or a clinically relevant model (Louie et al. 1986) have led to the conclusion that classic MDR was not a major mechanism of clinical drug resistance. It may therefore be desirable to extend cytotoxicity data surveys rather than to remain limited to gene expression. As drug resistance and metabolism are cell detoxification processes, it would be of interest to study the relationship between the overexpression of the P-glycoprotein and the possible amplification of cytochrome P-450 isozymes responsible for the metabolisation of vinca alkaloids.

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Correspondence and reprints: Dr *R. Rahmani*, INSERM U-278, Faculté de Pharmacie, 27 bd, Jean Moulin, 13385 Marseille, Cédex 5, France.

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Round-Table Discussion

Question: Dr Zhou, you comment that the intensity of cellular accumulation of vinca alkaloids may be related to their liposolubility. Does the liposolubility also influence the rate of efflux of vinca alkaloid from the cell?

Dr X.-J. Zhou: Liposolubility appears to influence both the rate and intensity of influx and efflux of vinca alkaloids.

Question: Does there appear to be any correlation between the member of the mdr1 gene family (i.e. mdr1a or mdr1b) amplified in a resistant cell line and the overall pattern of multiple drug resistance?

Dr Zhou: In humans, two P-glycoprotein genes are present (*mdr1* and *mdr3*), whereas there are 3 genes in mice (*mdr1a, mdr1b* and *mdr2*). cDNA transfection studies demonstrated that mouse MDR1a, MDR1b and human MDR1 can confer multidrug resistance. In contrast, human MDR3 or mouse MDR2 have, so far, failed to confer multidrug resistance.

Question: How do the pharmacokinetics and antitumour activity of oral vinorelbine compare with those of continuous infusion of vinorelbine?

Dr Zhou: Orally administered vinorelbine appears to retain most of the pharmacokinetic properties, side effects and presumably antitumour activity observed after bolus injection of the drug. Regarding continuous infusion, there are no pharmacokinetic data as yet, and only a few results are available concerning the antitumour activity of vinorelbine when given by this route. A recent study (Izzo et al. 1992) reported that, when administered by continuous infusion, vinorelbine was active against breast cancer. Positive clinical responses were obtained and included 5 complete remissions, 15 partial remissions, 7 minor remissions, 18 disease stabilisations and 22 disease progressions. However, more data are necessary to better characterise the antitumour activity, toxicity and pharmacokinetics of vinorelbine when administered by continuous infusion.

Question: Vinorelbine is a cell-cycle-dependent antimitotic agent. Do you think that short infusions of drug would achieve the clinical goal of maximising tumour cell toxicity and minimising adverse effects better than prolonged continuous infusions?

Dr Zhou: Short infusions of vinorelbine can avoid the very high initial concentrations achieved after bolus injections. In this context, it may be expected that short infusions will lead to fewer adverse effects but similar antitumour activity as compared with bolus injections. Appropriate long-term infusion can maintain a constant effective drug level and may presumably result in optimised antitumour activity.

Question: Dr Mouridsen, what considerations should be given to tumour receptor status when deciding which therapy to use in patients with breast cancer?

Dr H.T. Mouridsen: The response to endocrine therapy in advanced breast cancer is related to the receptor (estrogen or progesterone) status of the tumour. Thus, in receptor-positive tumours the chance of a response to endocrine therapy is approximately 50 to 60%, compared with less than 10% in receptor-negative tumours. Therefore, the estrogen receptor status should be used to select patients for first-line systemic therapy, endocrine therapy or chemotherapy. Patients known to be receptor-positive should be offered endocrine therapy.

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Those responding should also be offered a second-line endocrine therapy, whereas chemotherapy is the treatment of choice for the receptor-negative tumours and for the receptor-positive tumours unresponsive to first-line endocrine therapy.

In most cases, the definition of receptor status originates from analysis of the primary tumour; however, the available data indicate that there may be a 10 to 20% rate of conversion from receptor-positive status to receptor-negative status and vice versa. As a consequence, whenever feasible, selection of therapy according to receptor status should be based upon analysis of the status in the metastatic tissue.

Question: Are there any additional considerations when treating metastases in specific sites (e.g. bone, liver, brain)?

Dr Mouridsen: The response of metastases in various sites may vary between patients. It is unclear why the efficacy of systemic therapy varies in different sites, but it is plausible that tumour biology, local factors and methodological factors are involved. Thus, the available data on rates of response in relation to metastatic site have generally shown higher response rates in soft tissue metastases compared with visceral and bone metastases. It has been supposed that the blood-brain barrier may inhibit the diffusion of some agents into the cerebrospinal fluid. However, many studies have demonstrated that systemic therapy may also display activity in brain metastases that is similar to the activity observed in metastases outside the central nervous system (CNS).

There are no data to support the use of specific systemic therapies according to site of metastatic disease. However, for patients with extensive metastases in vital organs (e.g. the liver, lungs, or CNS), chemotherapy rather than endocrine therapy is usually recommended as the systemic treatment of choice because this approach offers the best possibility for the urgent relief of symptoms.

Question: What role does radiotherapy have in conjunction with chemotherapy or endocrine therapy in breast cancer?

Dr Mouridsen: Radiotherapy has a definite role in the treatment of locally recurrent or metastatic breast cancer.

In locally recurrent breast cancer in patients who have not had radiotherapy as part of the primary treatment, and who have no evidence of metastatic disease, radiotherapy is often administered with curative intent to the chest wall and regional lymph nodes.

For a larger proportion of patients with metastatic disease, there is a role for radiotherapy as a local palliative measure, in combination with systemic therapy. Patients with bone metastases giving rise to pain that cannot be controlled by medical analgesic therapy, patients with medullary compression or compression of peripheral nerves, and patients with CNS metastases would be expected to benefit from palliative radiotherapy.

Question: Prof. Marty, as single-agent treatment of advanced breast cancer, how does the tolerability profile of vinorelbine compare with the tolerability profiles of other, more traditional single agent regimens?

Prof. M. Marty: The trend in phase II studies has been to increase doses until clinically significant side effects are observed, and this has been the case with taxol, anthrapyrazoles and topoisomerase I inhibitors. Thus, it becomes difficult to compare the therapeutic index of vinorelbine with those of the more traditional single-agent therapies. The adverse effect profile of vinorelbine is dominated by rapidly reversible noncumulative neutropenia, which is amenable to prevention with colony stimulating factors.

Question: What was the rationale for selecting fluorouracil or doxorubicin as the second agent in vinorelbine combination regimens for the treatment of advanced breast cancer?

Prof. Marty: Fluorouracil and doxorubicin were selected for inclusion in combination therapy with the goals of providing adequate first-line therapy and studying an 'optimal' combination based upon the most active agents, i.e. anthracyclines and vinorelbine.

Question: What are some of the other chemotherapeutic agents currently being used in combination with vinorelbine in studies designed to eval-

uate the efficacy and safety of combination therapy in advanced breast cancer?

Prof. Marty: Other combinations currently being studied include combinations of vinorelbine with the following: fluorouracil and doxorubicin; ifosfamide; and thiotepa.

Question: Dr Cvitkovic, vinorelbine has achieved a good objective response rate for the treatment of inoperable non-small cell lung cancer (NSCLC). Does vinorelbine have a place as adjunctive therapy before or after the surgical removal of NSCLC?

Dr E. Cvitkovic: Chemotherapy before surgery or radiotherapy in patients with locoregionally advanced nonmetastatic NSCLC has been shown to be effective in stage IIIA and IIIB disease, both in open studies and in controlled randomised studies of active combinations of drugs. The experience to date with vinorelbine remains anecdotal, but it appears possible to assume that, as clinical experience with vinorelbine as a component of combination therapies in NSCLC accumulates, this agent will be used preoperatively in these patients.

Regarding postoperative adjuvant treatment, there is very little, if any, evidence that such treatment is beneficial in patients with NSCLC. It is certainly desirable to study the possibility of using vinorelbine as postoperative adjuvant therapy, but only in controlled clinical trials.

Question: How many cycles of vinorelbine as a continuous infusion are generally required to achieve a response in the treatment of breast cancer? Is this any different from the number of intravenous bolus cycles required?

Dr Cvitkovic: Responses have been achieved after 3 or 4 cycles of vinorelbine infusions. This does not differ from the number of cycles of vinorelbine administered by bolus injection. However, the data on bolus injections derived from phase II studies are rather poor.

Question: In phase II studies administering vinorelbine 30 mg/m^2/week intravenously, dose adjustment and/or treatment delay was required in 70% of patients. Does this imply that the recommended dosage of 30 mg/m^2/week is too high for most patients and, if so, are there any recommendations you would make for initiating therapy in the clinical setting?

Dr Cvitkovic: Only 15 to 25% of patients are able to receive vinorelbine 30 mg/m^2/week without interruption, and it appears that a dose of 24 to 26 mg/m^2/week would be compatible with outpatient administration. However, the dose used should be active and compatible with combined chemotherapy. The maximal dose that can be used in this setting is highly dependent on the type and stage of disease, characteristics of the patient population, other agents included in the combination, administration of haematopoietic growth factors, and the intention of treatment (palliative or curative). We have observed that vinorelbine 18 mg/m^2 is beneficial when administered on days 1 and 8 of each 3-week cycle in combination with cisplatin/fluorouracil/folinic acid, and that the results observed with this dose are similar to those observed by other investigators using higher doses. Recent Japanese experience has yielded similar results with vinorelbine 20 mg/m^2/week for the treatment of NSCLC.

To summarise, there is a need for further research into the potential, synergistic activity and dose-response relationship of vinorelbine.

Question: Dr Sørensen, what are the usual survival times in treated *vs* untreated small cell lung cancer (SCLC) and NSCLC?

Dr J.B. Sørensen: The survival time in SCLC was 1.5 to 3 months before the introduction of chemotherapy (Hansen 1987). Since the introduction of combination chemotherapy, the median survival time has increased 5-fold. The 2 key factors predicting survival are pretreatment performance status and extent of disease, and the median survival time is now about 9 months and 14 months in patients with extensive and limited disease, respectively (Østerlind & Andersen 1986).

The survival times in patients with inoperable NSCLC receiving the best supportive care only have been compared with the rates observed in patients receiving combination chemotherapy in several studies. The median survival time ranged from 10 to 17 weeks for patients receiving the best supportive care in 3 recent studies (Quoix et al. 1991; Rapp

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Question: Is the introduction of new drugs such as 5-HT_3-receptor antagonists and colony-stimulating factors likely to affect the prognosis in patients with lung cancer, by allowing more intensive regimens?

Dr Sørensen: New drugs such as 5-HT_3-receptor antagonists and colony stimulating factors have been valuable additions to available supportive care, since they have reduced gastrointestinal side effects and myelotoxicity. However, until now there has not been a major effect on treatment outcome with respect to increased response rate or survival associated with these agents. Given the current status of chemotherapy in NSCLC, it is unlikely that these new drugs will result in a better prognosis, but further evaluation of colony-stimulating factors in SCLC might contribute to more active treatments, although research is still at the experimental level.

Question: Can you provide more details of the adverse effects of vinorelbine? Has neurotoxicity ever been reported?

Dr Sørensen: A few cases of neurotoxicity have been reported (Besenval et al. 1991). Among 26 breast cancer patients treated with vinorelbine 30 mg/m² weekly, one patient had WHO grade 3 peripheral neuropathy, which was reversed when treatment was discontinued. One of 78 patients with NSCLC treated with vinorelbine 30 mg/m²/week developed paralytic ileus. This effect was also reversed completely. In addition, 9 cases of muscle weakness (WHO grade 3) were noted in patients treated with vinorelbine for 3 to 6 months.

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